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A New Type of C_2-Symmetric Bisphospine Ligands with a Cyclobutane Backbone: Practical Synthesis and Application

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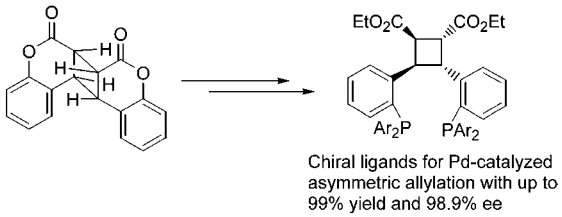
ABSTRACT



Chiral ligands for Pd-catalyzed asymmetric allylation with up to 99% yield and 98.9% ee

A highly efficient and practical optical resolution of anti-head-to-head racemic coumarin dimer, (±)-5, by molecular complexation with TADDOL (6) through hydrogen bonding and a convenient transformation of enantiopure 5 to a new type of C_2-symmetric bisphosphine ligand (3) have been achieved. The asymmetric induction efficiency of these chiral bisphosphine ligands was evaluated in Pd-catalyzed asymmetric allylic substitution, affording the allylic substitution products in excellent yield (up to 99%) and enantioselectivity (up to 98.9% ee).

Asymmetric catalysis of organic reactions to provide enantiomerically enriched products is of central importance to modern synthetic and pharmaceutical chemistry.[1] Development of chiral ligands is one of the most fascinating methods to achieve high enantioselectivity of a given catalytic asymmetric reaction.[2] Therefore, the need for the design of novel chiral ligands has been an eternal theme for organic chemists. On the basis of the fact that some C_2-symmetric bisphosphine ligands (such as BINAP,[3] Trost's ligand (**1**),[4] and so on) showed excellent asymmetric induction in many kinds of asymmetric reactions, we are interested in the development of a new-type of C_2-symmetric bisphosphine ligand (**3**) with a cyclobutane backbone, which can be considered as an analogue of **1** and **2**.[5] In this paper, we report the first synthesis of **3** and its application to Pd-catalyzed asymmetric allylic substitution. An efficient and practical resolution of anti-head-to-head racemic coumarin dimer (±)-**5** has also been achieved by molecular complexation with (*R*,*R*)-(−)-*trans*-bis(hydroxyldiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane (TADDOL, **6**) to give enantiopure **5**, a key intermediate for the synthesis of **3**.

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(3) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40.

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(5) (a) Hayashi, M.; Hashimoto, Y. Takezaki, H.; Watanabe, Y.; Saigo, K. *Tetrahedron*: *Asymmetry* **1998**, *9*, 1863. For the examples of bisphosphine ligands with five-membered ring backbones, see: (b) Fukuda, N.; Mashima, K.; Matumura, Y.; Takaya, H. *Tetrahedron Lett.* **1990**, *31*, 7185. (c) Terfort, A.; Brunner, H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1467.

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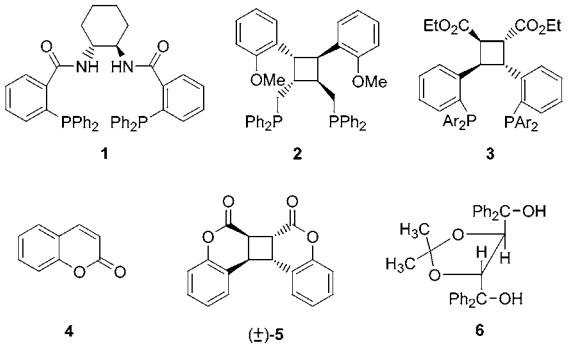
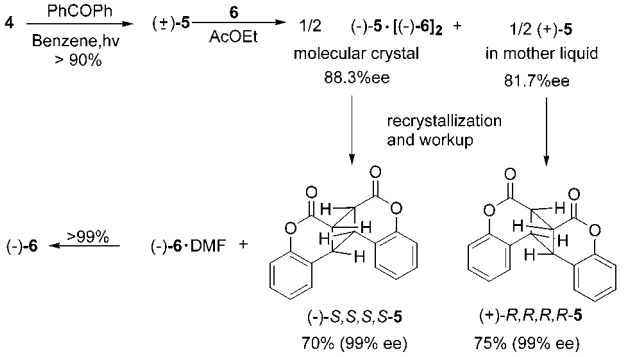


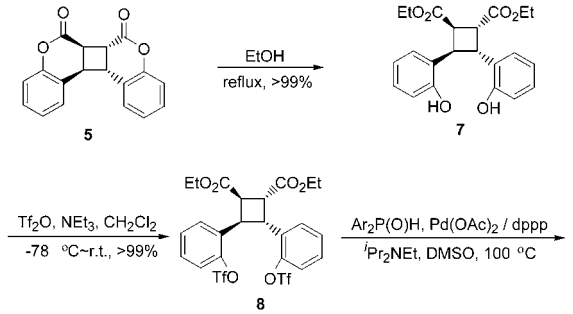
As shown in Scheme 1, the preparation of anti-head-to-head racemic coumarin dimer (±)-**5** was carried out following a literature method by irradiation of coumarin **4** in benzene solution in the presence of benzophenone as a sensitizer in >90% yield (0.2 mol scale).[6] Although the optical resolution of (±)-**5** could be achieved by stepwise recrystallization of its diastereomers formed with enantiopure α-phenylethamine, followed by acidic hydrolysis and recyclization of hydroxy acid,[7] the process is somewhat long. Direct synthesis of enantiopure **5** through a topochemical-controlled [2 + 2] photodimerization of coumarin **4** included in TADDOL (**6**) host in the solid state or in aqueous suspension was recently reported by Toda, giving (−)-**5** in 99% yield with 100% ee.[8] Despite the difficulty of large-scale preparation using this strategy, the perfect molecular recognition between **6** and (−)-**5** in the product prompted us to utilize easily available **6**[9] as a chiral host to resolve two enantiomers of **5** by molecular complexation through hydrogen bonding. Heating a mixture of an equal molar amount of (±)-**5** and resolving agent **6** in ethyl acetate, followed by cooling the homogeneous solution to room temperature, resulted in the formation of molecular crystals between **6** and (−)-**5** with 88.3% ee of (−)-**5**. The precipitated crystals were collected by filtration and washed with ethyl acetate, which were characterized as 2:1 molecular crystals of **6** and (−)-**5** by ^{1}H NMR. The enantiomeric excess of the opposite enantiomer ((+)-**5**) that remained in mother liquid was 81.7%. Further recrystallization of the molecular crystals (−)-**5**·[**6**]$_2$ from ethyl acetate afforded enantiopure (−)-**5**·[**6**]$_2$ in 70% yield. Decomposition of the molecular crystals (−)-**5**·[**6**]$_2$ with DMF gave (−)-**5** and **6**·DMF complex in quantitative yields. The absolute configuration of (−)-**5** was assigned to be *S*,*S*,*S*,*S* by comparison of its optical rotation with that reported in the literature.[8a] The enantiomeric excess of (+)-**5** in the mother liquid could be further enriched to 99% by recrystallization from ethanol. The resolving agent **6** could be recovered in >99% yield by decomposition of molecular crystals, **6**·DMF, in water and followed by extraction with ethyl acetate (see the Supporting Information).

Scheme 1. Practical Optical Resolution of Coumarin Dimer with TADDOL by Molecular Complexation



With enantiopure **5** in hand, we extended its application to the synthesis of a new type of C_2-symmetric bisphosphine ligand **3**. As shown in Scheme 2, refluxing ethanol solution

Scheme 2. Transformation of Enantiopure Coumarin Dimer (**5**) to a New Type of Chiral Bisphosphine Ligands (**3a**−**f**)



a: Ar=Ph (99%);
b: Ar = 3,5-$(CH_3)_2C_6H_3$(95%)
c: Ar = 4-$CH_3C_6H_4$ (83%)
d: Ar = 3-$CH_3C_6H_4$ (97%)
e: Ar = 4-$CH_3OC_6H_4$ (88%)
f: Ar = 4-$(CH_3)_3CC_6H_4$ (92%)

a: Ar=Ph (74%);
b: Ar = 3,5-$(CH_3)_2C_6H_3$(74%)
c: Ar = 4-$CH_3C_6H_4$ (76%)
d: Ar = 3-$CH_3C_6H_4$ (76%)
e: Ar = 4-$CH_3OC_6H_4$ (80%)
f: Ar = 4-$(CH_3)_3CC_6H_4$ (91%)

of **5** resulted in the lactone ring opening to give ethyl ester **7** in quantitative yield. Treatment of **7** with $(CF_3SO_2)_2O$ in the presence of Et_3N gave its ditriflate derivative **8** quantitatively. Compound **8** underwent a coupling reaction with diarylphosphine oxides in the presence of Pd(OAc)$_2$/dppp (dppp = 1,3-bis(diphenyl-phosphino)propane) and diisopropylethylamine to give corresponding 1,2-bis(2-diarylphosphinylphenyl)cyclo-butane derivatives **9a**−**f** in good to excellent yields.[10] The target bisphosphine ligands **3a**−**f** were easily obtained by the reduction of their oxides **9a**−**f** with $HSiCl_3$ in the presence of *N*,*N*-dimethylaniline in 74−91% yields.

Pd-catalyzed enantioselective allylic substitution is one of the most important C−C or C−N bond forming reactions

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(8) (a) Tanaka, K.; Toda, F.; Mochizuki, E.; Yasui, N.; Kai, Y.; Miyahara, I.; Hirotsu, K. *Angew. Chem., Int. Ed.* **1999**, *39*, 3523. (b) Tanaka, K.; Toda, F. *J. Chem. Soc., Perkin Trans. 1* **1992**, 943.
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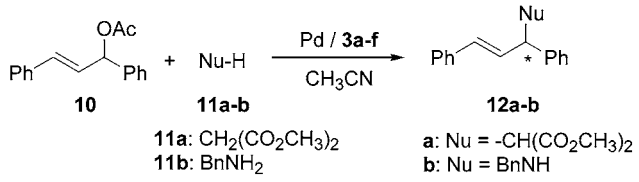
in modern asymmetric catalysis.[11] To demonstrate the asymmetric induction efficiency of the chiral ligands **3a**−**f**, Pd-catalyzed enantioselective allylic substitution was taken as a model reaction. 1,3-Diphenylprop-2-enyl acetate (**10**) was employed as the substrate, and dimethylmalonate **11a** and benzylamine **11b** were utilized as nucleophiles, respectively. As shown in Table 1, all of the chiral ligands (**3a**−**f**)

Table 1. Pd/**3**-Catalyzed Enantioselective Allylic Substitutions[a]



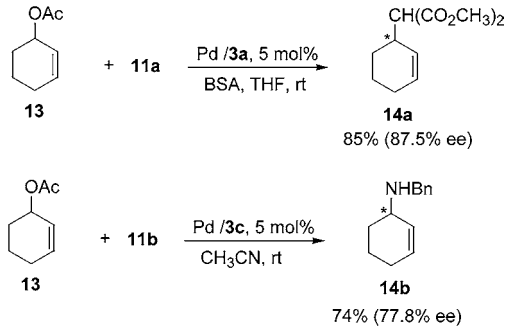
entry	ligand	base	NuH	product	yield[b] (%)	ee[c] (%)
1	**3a**	BSA	**11a**	**12a**	99	96.8
2	**3b**	BSA[d]	**11a**	**12a**	99	97.3
3	**3c**	BSA[d]	**11a**	**12a**	99	95.8
4	**3d**	BSA[d]	**11a**	**12a**	99	96.1
5	**3e**	BSA[d]	**11a**	**12a**	99	98.0
6	**3f**	BSA[d]	**11a**	**12a**	99	97.5
7	**3f**	BSA	**11a**	**12a**	99	98.9
8	**3a**		**11b**	**12b**	99	95.6
9	**3b**		**11b**	**12b**	94	96.7
10	**3c**		**11b**	**12b**	91	97.5
11	**3d**		**11b**	**12b**	96	96.4
12	**3e**		**11b**	**12b**	91	96.2
13	**3f**		**11b**	**12b**	97	96.2

[a] Molar ratio of **10**/NuH/[η-allylPdCl]$_2$/**3** = 1:2:0.025:0.06. [b] Isolated yield. [c] Determined with HPLC on a Chiralcel OJ or AD column. [d] 2 equiv of BSA was added in the presence of 5 mol % of LiOAc.

showed excellent asymmetric induction in the model reaction to give corresponding allylation products in 91−99% yields with 95.6−98.9% ee.

The extension of the present catalyst system to the allylic substitution of cyclic substrate **13**[12] (Scheme 3) demonstrated that the reaction proceeded smoothly to give the corresponding cyclic allylation products **14a** and **14b** in good yields (70−85%) and enantioselectivities (77.8−87.5% ee) using 5 mol % of the catalysts.

Scheme 3. Pd/**3**-Catalyzed Enantioselective Allylic Substitutions of Cyclic Substrate



In summary, a highly efficient and practical optical resolution of anti-head-to-head racemic coumarin dimer **5** by molecular complexation with TADDOL **6** through hydrogen bonding and a convenient transformation of enantiopure **5** to a new type of C_2-symmetric bisphosphine ligand **3**, have been achieved.[13] The asymmetric induction efficiency of these chiral bisphosphine ligands was evaluated in Pd-catalyzed asymmetric allylic substitution. Under the experimental conditions, the allylic substitution products could be obtained in excellent yield (up to 99%) and enantioselectivity (up to 98.9% ee). The research on the application of **3** to other asymmetric reactions and development of polymer-supported bisphosphine ligands[14] by taking the advantage of easily derived carboxylate groups at the backbone of cyclobutane is underway in this laboratory.

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Supporting Information Available: Spectral characterization of the products and experimental details for asymmetric reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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